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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,703	05/25/2006	Linglong Zou	12279-185-999	5032

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Nikolaos C. George
JONES DAY
222 E. 41st. Street
New York, NY 10017-6702

EXAMINER	
KINSEY WHITE, NICOLE ERIN	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
08/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,703	ZOU ET AL.	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-42* is/are pending in the application.

4a) Of the above claim(s) *32-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-31,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election of Group I (claims 21-31 and new claims 41 and 42) in the reply filed on April 21, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Objections

Claim 21 is objected to because of the following informalities: Claim 21 is missing the word "and" after part a. In addition, claim 21 should recite "compound or combination of compounds" in stead of "compound(s)" in part b of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites that the second cell line expresses CD4 and its co-receptors. It is not clear what constitutes co-receptors for CD4. Do applicants mean gp120 co-receptors?

Claim 27 also recites that synergism occurs if the level of expression in (i) is less than the additive level of expression for each compound in (ii), as compared to the level of expression in (iii). This is not clear. For example, if part (iii), which has no inhibitor present has a β-gal expression level of 100%, and part (ii) has a β-gal expression level of 50% for compound A alone and 30% for compound B alone, and part (i), the combination of compounds A and B, has a β-gal expression level of 70%. Here, part (i) has a β-gal expression level that is less than the additive level of each compound in (ii) (30% + 50%), however, part (i) has a β-gal expression level that is higher than each compound alone. According to the claim language, this means inhibitory synergism occurred. Clearly, compounds A and B had an inhibitory effect because the level of β-gal expression decreased from 100% for each, but there is no synergism. For inhibitory synergism to occur, the β-gal expression level of part (i) should be lower than the β-gal expression level of either compound A alone or compound B alone (i.e., a further decrease in β-gal expression when compared to either compound alone).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21-23, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Takashima et al. (Antimicrobial Agents and Chemotherapy, 2001,

45(12):3538–3543) as evidenced by Carnec et al. (Journal of Virology, 2005, 79(3):1930-1933).

The claims are directed to a method for assaying a compound or combination of compounds capable of inhibiting Human Immunodeficiency Virus ("HIV') entry into a cell comprising:

a. co-cultivating a first cell line expressing a gpl20-gp41 complex on its cell surface and comprising an inducer, and a second cell line expressing CD4 and CXCR4 its co receptors on its cell surface and comprising a reporter gene, the expression of which is induced by the inducer of the first cell line, in the presence of a compound or combination of compounds under conditions that allow cell fusion; and

b. comparing the level of expression of the reporter gene in the presence of said compound(s) with the level of expression of the reporter gene in the absence of said compound(s).

Takashima et al. discloses a cell-cell fusion assay to test the inhibitory effects of small molecule CCR5 antagonists. The fusion assay comprises a 293T cell expressing Tat and Env and MAGI-CCR5 cells (a HeLa cell line expressing CCR5) expressing CD4 and containing a β-galactosidase gene controlled by the HIV LTR (see Figure 2). It is well known in the art that HeLa cells naturally express CXCR4 (see Carnec et al. page 1930, left column). Takashima et al. also teaches that the fusion assay can also be used to evaluate CXCR4 antagonists. The antagonist was tested at different concentrations (see Figure 3).

Claims 21-23, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Moir et al. (AIDS Research and Human Retroviruses, 1996, 12(9):811-820) as evidenced by Carnec et al. (Journal of Virology, 2005, 79(3):1930-1933).

Moir et al. discloses a cell-cell fusion assay to test the inhibitory effects of antibodies. The fusion assay comprises A2.01 expressing Env and tat and HeLa cells expressing CD4 and the β-gal gene controlled by the HIV LTR. It is well known in the art that HeLa cells naturally express CXCR4 (see Carnec et al. page 1930, left column). The antibodies were tested at different concentrations (see page 813, left column).

Claims 21-23, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Chiba et al. (The Journal of Antibiotics, 2001, 54(10):818-826) as evidenced by Carnec et al. (Journal of Virology, 2005, 79(3):1930-1933).

Chiba et al. discloses a cell-cell fusion assay to test the inhibitory effects of potential anti-HIV drugs. The fusion assay comprises HeLa cells expressing CD4 and LTR-β-gal (or HOS cells expressing CD4, CCR5 and LTR-β-gal) and HeLa cells expressing Env and tat. It is well known in the art that HeLa cells naturally express CXCR4 (see Carnec et al. page 1930, left column). The drugs were tested at different concentrations.

Claim 21 is rejected under 35 U.S.C. 102(b) as being anticipated by Rucker et al. (Methods in Enzymology, 1997, 288:118-133).

Rucker et al. discloses a fusion assay to test the effects of inhibitors on HIV fusion and/or replication. The assay comprises an effector cell line, typically HeLa cells, expressing HIV envelop proteins and T7 polymerase, a target cell line expressing CD4, a chemokine receptor such as CXCR4 or CCR5, and a luciferase reporter gene under the control of the T7 promoter. Upon fusion, luciferase expression is induced by T7 polymerase activity on the T7 promoter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 27-31, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takashima et al. (Antimicrobial Agents and Chemotherapy, 2001,

45(12):3538–3543) as evidenced by Carnec et al. (Journal of Virology, 2005, 79(3):1930-1933) and in view of Nagashima et al. (Journal of Infectious Disease, 2001, 183:1121-1125).

The claims are directed to a method for assaying for a synergistic combination of compounds capable of inhibiting Human Immunodeficiency Virus ("HIV") entry into a cell comprising:

a. co-cultivating a first cell line expressing a gpl20-gp41 complex on its cell surface and comprising an inducer, and a second cell line expressing CD4 and its co-receptors on its cell surface and comprising a reporter gene, the expression of which is induced by the inducer of the first cell line,

i. in the presence of a combination of compounds;

ii. in the presence of each individual compound of the combination alone; and

iii. in the absence of any compound; and

b. comparing the level of expression of the reporter gene for each of (i), (ii), and (iii),

wherein a combination of compounds is synergistic if the level of expression in (i) is less than the additive level of expression for each compound in (ii), as compared to the level of expression in (iii).

The teachings of Takashima et al. and Carnec et al. outlined above. Takashima et al. and Carnec et al. do not teach a method for assaying for a synergistic combination

of compounds. However, Nagashima et al. teaches a cell-cell fusion assay to assay for synergistic activity between HIV entry/fusion inhibitors. The assay comprises fluorescently labeled cell lines, one cell line expressing HIV Env and a second cell line expressing CD4, CCR5 and CXCR4. Upon fusion, fluorescence occurs. Nagashima et al. used this assay to determine synergy between two HIV fusion inhibitors, PRO 542 and T-20.

It would have been obvious to one of ordinary skill in the art to modify the method taught by Takashima et al. and use the assay to determine synergism. One would have been motivated to do so given the suggestion by Nagashima et al. that cell-cell fusion assays comprising a reporter can be used to make such a determination. There would have been a reasonable expectation of success given the fact that Nagashima et al. successfully used a cell-cell based fusion assay to determine synergy between two HIV fusion inhibitors, PRO 542 and T-20.

As for the various claimed cell types and reporter genes, it is well within the purview of one of ordinary skill in the art to substitute one cell type for another or one reporter gene/inducer combination for another and the results would have been predictable.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 21-31, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jenkinson et al. (Journal of Biomolecular Screening, 2003, 8(4):463-470) in view of Nagashima et al. (Journal of Infectious Disease, 2001, 183:1121-1125).

Jenkinson et al. teaches a cell-cell fusion assay to determine the effect of a compound on HIV fusion. The assay comprises HEK cells expressing tat, rev and gp160 and HOS cells expressing CCR5, CD4 and HIV-LTR-Luciferase. Upon fusion, luciferase expression is induced by tat. Jenkinson et al. does not teach the claimed cell types, CXCR4, β-gal, or a method for assaying for a synergistic combination of compounds. However, Nagashima et al. teaches a cell-cell fusion assay to assay for synergistic activity between HIV entry/fusion inhibitors. The assay comprises fluorescently labeled cell lines, one cell line expressing HIV Env and a second cell line expressing CD4 and CCR5 and CXCR4. Upon fusion, fluorescence occurs. Nagashima et al. used this assay to determine synergy between two HIV fusion inhibitors, PRO 542 and T-20.

It would have been obvious to one of ordinary skill in the art to modify the method taught by Jenkinson et al. and use the assay to determine synergism. One would have been motivated to do so given the suggestion by Nagashima et al. that cell-cell fusion assays comprising a reporter can be used to make such a determination. There would have been a reasonable expectation of success given the fact that Nagashima et al. successfully used a cell-cell based fusion assay to determine synergy between two HIV fusion inhibitors, PRO 542 and T-20.

As for the various claimed cell types, chemokine receptors and reporter genes, it is well within the purview of one of ordinary skill in the art to substitute one cell type for another, one reporter gene/inducer combination for another or one HIV co-receptor for another depending on the virus tropism and the results would have been predictable.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 24, 27-31, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moir et al. (AIDS Research and Human Retroviruses, 1996, 12(9):811-820) as evidenced by Carnec et al. (Journal of Virology, 2005, 79(3):1930-1933) and in view of Nagashima et al. (Journal of Infectious Disease, 2001, 183:1121-1125).

The teachings of Moir et al. and Carnec et al. outlined above. Moir et al. and Carnec et al. do not teach a method for assaying for a synergistic combination of compounds. However, Nagashima et al. teaches a cell-cell fusion assay to assay for synergistic activity between HIV entry/fusion inhibitors. The assay comprises fluorescently labeled cell lines, one cell line expressing HIV Env and a second cell line expressing CD4, CCR5 and CXCR4. Upon fusion, fluorescence occurs. Nagashima et al. used this assay to determine synergy between two HIV fusion inhibitors, PRO 542 and T-20.

It would have been obvious to one of ordinary skill in the art to modify the method taught by Moir et al. and use the assay to determine synergism. One would have been

motivated to do so given the suggestion by Nagashima et al. that cell-cell fusion assays comprising a reporter can be used to make such a determination. There would have been a reasonable expectation of success given the fact that Nagashima et al. successfully used a cell-cell based fusion assay to determine synergy between two HIV fusion inhibitors, PRO 542 and T-20.

As for the various claimed cell types and reporter genes, it is well within the purview of one of ordinary skill in the art to substitute one cell type for another or one reporter gene/inducer combination for another and the results would have been predictable.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 24, 27-31, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiba et al. (The Journal of Antibiotics, 2001, 54(10):818-826) as evidenced by Carnec et al. (Journal of Virology, 2005, 79(3):1930-1933) and in view of Nagashima et al. (Journal of Infectious Disease, 2001, 183:1121-1125).

The teachings of Chiba et al. and Carnec et al. outlined above. Chiba et al. and Carnec et al. do not teach a method for assaying for a synergistic combination of compounds. However, Nagashima et al. teaches a cell-cell fusion assay to assay for synergistic activity between HIV entry/fusion inhibitors. The assay comprises fluorescently labeled cell lines, one cell line expressing HIV Env and a second cell line expressing CD4, CCR5 and CXCR4. Upon fusion, fluorescence occurs. Nagashima et

al. used this assay to determine synergy between two HIV fusion inhibitors, PRO 542 and T-20.

It would have been obvious to one of ordinary skill in the art to modify the method taught by Chiba et al. and use the assay to determine synergism. One would have been motivated to do so given the suggestion by Nagashima et al. that cell-cell fusion assays comprising a reporter can be used to make such a determination. There would have been a reasonable expectation of success given the fact that Nagashima et al. successfully used a cell-cell based fusion assay to determine synergy between two HIV fusion inhibitors, PRO 542 and T-20.

As for the various claimed cell types and reporter genes, it is well within the purview of one of ordinary skill in the art to substitute one cell type for another or one reporter gene/inducer combination for another and the results would have been predictable.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White, PhD/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648